Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-123 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-123 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-123 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

The Examiner asserts that the specification does not disclose a function for the antibodies of SEQ ID NO: 399. For the reasons outlined below, Applicants respectfully disagree.

Utility Guidelines

In interpreting the utility requirement, in *Brenner v. Manson* [1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form." [2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy." [3]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

Later, in *Nelson v. Bowler*[4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6] the CAFC reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the

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[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[10] *Ibid.*

utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." [11, 12]

Compliance with 35 U.S.C. §101 is a question of fact. [13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. [14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines") [15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on

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[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

[12] *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial' utility."" [16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, [17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Arguments

Applicants maintain that the specification provides sufficient disclosure to establish a specific, substantial and credible utility for the instantly claimed PRO1187 antibodies of SEQ ID NO: 399.

The Examiner says on Page 5 of the final Office action that "the Examiner did not acknowledge that the nucleic acid encoding PRO1187 showed a positive correlation for lung and colon cancer".

Applicants submit that there is a positive correlation for lung cancer and the gene encoding PRO1187 based on the gene amplification data, which is an essential mechanism for oncogene activation and is well-described in Example 170, page 539 of the present application. The gene amplification data shows that genomic DNA was isolated from a variety of primary cancers and cancer cell lines listed in Table 9 (especially page 554, Table 9C) which includes primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9C. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added).

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[16] M.P.E.P. §2107.01.

Table 9C indicates that PRO1187 showed approximately 1.17-1.55 ΔCt units which corresponds to $2^{1.17}$-$2^{1.55}$- fold amplification or **2.25- fold to 2.928-fold** amplification in squamous cell carcinomas of lung (see Table 8, page 546). These values are considered significant based on the Declaration by Dr. Audrey Goddard (submitted herewith). Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, **2.25- fold to 2.928-fold** amplification in squamous cell carcinomas of lung would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration and therefore, barring evidence to the contrary, Applicants maintain that the fold amplification disclosed for the PRO1187 gene is significant and forms the basis for the utility claimed herein.

A *prima facie* case of lack of utility has not been established

Further, the Examiner says on Page 5 of the final Office action that "the Examiner is not questioning whether the asserted utility is credible. The question is whether the asserted utility is specific or substantial". The Examiner maintains that, based on the "disclosure in the art such as Haynes *et al.*, Pennica *et al.* and Konopka *et al.*, there is not always such a correlation, the skilled artisan....would perform the experiment to verify it.....it is not the norm that gene amplification, or even increased trancription, results in increased protein levels". Applicants respectfully disagree.

[17] M.P.E.P. §2107 II (B) (1).

Firstly, Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene" in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. Similarly Konopka only addresses the *abl* gene, again not genes in general, and is therefore not an appropriate reference for making a *prima facie* case for lack of utility. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica and Konopka teach nothing of the correlation between gene amplification and polypeptide over-expression in general.

Applicants also respectfully point out that, in fact, Haynes teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (see Figure 1) (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, Haynes shows that there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the Figure shows that the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." But, it is not a legal requirement to accurately predict protein levels from the evidence presented nor to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels, as discussed above. Moreover, in Figure 1 or Haynes, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Therefore, the Haynes data, in fact, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Thus, Applicants submit that the Examiner's rejection is based on a misunderstanding of the scientific data presented in Haynes *et al.*

Therefore, contrary to the Examiner's assertion, the cited art does not support the teaching that "nucleic acid copy number is not predictive of a similar association for protein" in general.

In fact, Pennica's, Konopka's and Haynes' teachings do not provide sufficient reasons to doubt the Applicants statements regarding PRO1187's utility as a marker to diagnose lung cancer.

In fact, the correct test for utility is whether it is "more likely than not" that, a positive correlation exists between proteins and nucleic acid levels. Based on the teachings of Ornfoft *et al.*, Pollack *et al.* and Hyman *et al.* (previously submitted) and the Haynes reference cited by the Examiner, a vast number of genes studied in these references indicated that "there was a general trend between increased protein expression and transcript levels," which meets the "more likely than not" standard and clearly shows that increased gene levels correlate well, in most genes, with increased expression of the protein.

The Examiner considered the three references Ornfoft *et al.*, Pollack *et al.* and Hyman *et al.* but states that these references "do not appear to look at a single gene at a time".

Applicants respectfully point out that in Ornfoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornfoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornfoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornfoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornfoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornfoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornfoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. The Examiner has stated that Applicants have not indicated whether PRO341 is in a gene cluster region of a

chromosome. Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters.

Applicants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs was hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also

done on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

Applicants further submit that, even if there were no correlation between gene amplification and increased mRNA/ protein expression, (which Applicants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Applicants previous Response filed June 18, 2004) explains:

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Additional supporting evidence for such a utility is presented in a real-world example in an article by Hanna and Mornin (submitted with Applicants' Response filed June 4, 2004), which demonstrates a use for the breast cancer marker HER-2/neu. Hanna and Mornin teach that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH), as well as, the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Thus, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin, one skilled in the art would appreciate that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not over-expressed. This leads to better determination of a suitable therapy for the tumor. Such testing is for the purpose of characterizing not the PRO1187 polypeptide, but the tumors in which the gene encoding PRO1187 is amplified. Therefore, the PRO1187 polypeptide is also useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Based on the gene amplification data presented for PRO1187 in Example 170 of the specification, and all the submitted evidence, there is ample support for the Applicants' position that increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels. One of skill in the art would therefore reasonably expect, based on: (a) the

gene amplification data for the PRO1187 gene, (b) the supportive evidence in the Declarations submitted, and, (c) the supportive articles presented by the Applicants which were available in the art at the time of filing of the instant application, that the PRO1187 polypeptide is most likely, concomitantly, overexpressed in certain lung tumors, just like the PRO1187 gene, and is therefore useful as a tumor marker for certain lung cancers. Even in the event that the PRO1187 polypeptide were found not to be overexpressed in the lung tumors where the PRO1187 gene were amplified, (a position expressly not conceded to), the PRO1187 polypeptide is still useful as a marker in tumor categorization and becomes an useful tool, enabling the physician to decipher appropriate lines of treatment for the cancer patient, which is a real-life utility.

This opinion expressed by Dr. Ashkenazi in his Declaration, who is an expert in the field of Cancer biology and is a Director of Molecular Oncology at Genentech, Inc. and by Dr. Polakis are based on their own factual findings. Dr Ashkenazi's Declaration is supported by Hanna and Mornin's HER-2 gene/ neu protein study. Moreover, the case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew. [18] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" [19] Furthermore, the Federal Court of Appeals held in *In re Alton*, "[w]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" [20] Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines [21] which states that,

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

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[18] *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (CCPA 1976) and *In re Piasecki* 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[19] *In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker* 977 F 2d at 1445, u2 USPQ2d at 1444.

[20] *In re Alton*, supra.

[21] Part IIB, 66 Fed. Reg. 1098 (2001).

Therefore, barring evidence to the contrary regarding the Ashkenazi and Polakis declarations, this rejection is improper under both the case law and the Utility guidelines.

Thus, Applicants submit that they have demonstrated utility for the PRO1187 polypeptide as a lung tumor marker based on gene amplification evidentiary data in the specification, and also based on supportive literature which was available to one of skill in the art at the time of filing. Moreover, the Patent Office has failed to meet its initial burden of proof that the Applicant's claims of utility are not "substantial" or "specific" based on the prior art papers presented by the Examiner, since they do not address general trends or genes "in general" and instead address isolated cases.

Applicants further submit that based on the claimed utility for PRO1187 antibodies in the diagnosis of lung cancer, and the collective teachings in the specification, one of skill in the art would know exactly how to make and use the claimed polypeptide for the diagnosis of lung cancer. Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility and enablement rejections should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C41).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 1, 2005

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